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## **DEVELOPMENT OF A PROCESS ANALYTICAL TECHNOLOGY (PAT) INFRASTRUCTURE FOR FUTURE BIOLOGICS UPSTREAM PROCESSING**

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**Key Words:** Process Analytical Technology (PAT), bioreactor, online monitoring, process control,

Process Analytical Technology (PAT) involves the timely analysis of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) with the aim to improve the process control strategy resulting in a better process performance and robust product quality. The progress of PAT implementation in upstream bioprocessing has been slow mainly due to the complexity of the process steps with many parameters involved, and the complexity of the product and the culture medium. While the first approved PAT-based Real Time Release application in the small molecules field already celebrating its 10th anniversary in 2016, PAT for upstream bioprocessing is only now maturing.

This paper will discuss the considerations and constraints during design, construction and early operation of a PAT system at MSD in Oss (Part of Merck & Co), The Netherlands. A four-stage strategy is adopted. The first stage brings routine in process analyses online. This is achieved by linking an auto-sampler to a cell counter and a nutrient analyzer. This setup will already reduce manual sampling needs and increase process understanding. In the second stage these online nutrient measurements are used to control feeding at a target glucose concentration (feedback control loop). In the third stage online CQA measurements on the cell containing culture broth are added to gain high resolution information on CQA evolution during the culture process. In the fourth stage online spectroscopic tools are added to replace sample-based methods such as nutrient analysis and cell counts. In parallel an IT infrastructure is built to support online data modelling and model-based feedback control. The final system is very advanced in its kind and will potentially have real time release capability for the upstream harvest. This strategy, the system design and layout of the PAT infrastructure at MSD in Oss will be presented as well as experimental results and system performance data.